Current Management of IPF and fibrosing ILDs

Dr R Lakshmi Narasimhan
Dept of Pulmonary Medicine

Introduction

- Idiopathic pulmonary fibrosis – clinical course is variable and long term survival is poor
- Therapy – elusive & controversial
- Disease continues to progress with lung transplantation as the only measure to prolong survival

HRCT Pattern*	Surgical Lung Biopsy Pattern* (When Performed)	Diagnosis of IPF?†
UIP	**UIP** **Probable UIP** **Possible UIP** **Nonclassifiable fibrosis‡**	**YES**
	Not UIP	No
Possible UIP	**UIP** **Probable UIP**	**YES**
	Possible UIP Nonclassifiable fibrosis	Probable§
	Not UIP	No
Inconsistent with UIP	UIP	Possible§
	Probable UIP Possible UIP Nonclassifiable fibrosis Not UIP	No

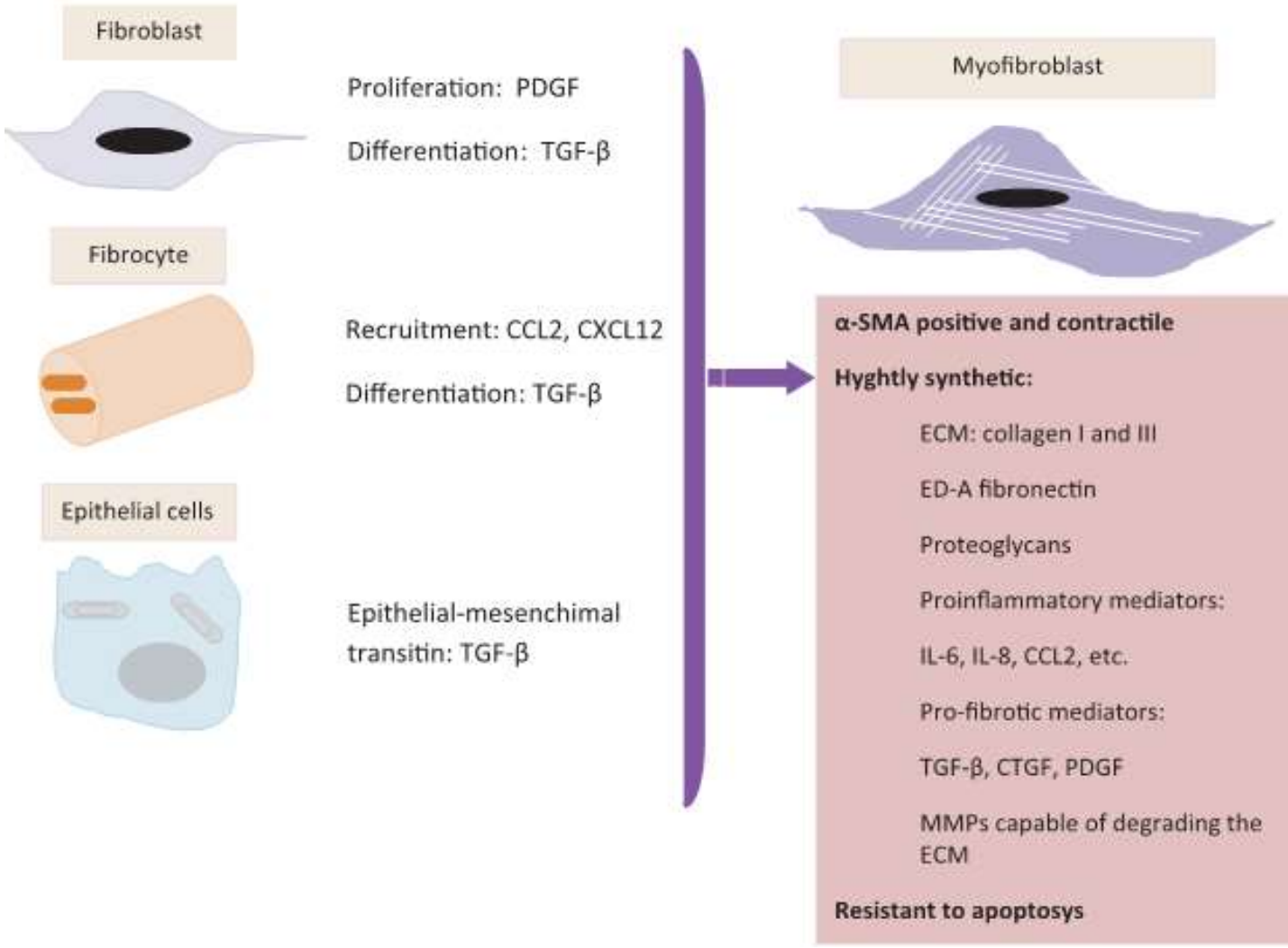
American Thoracic Society Documents

An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management

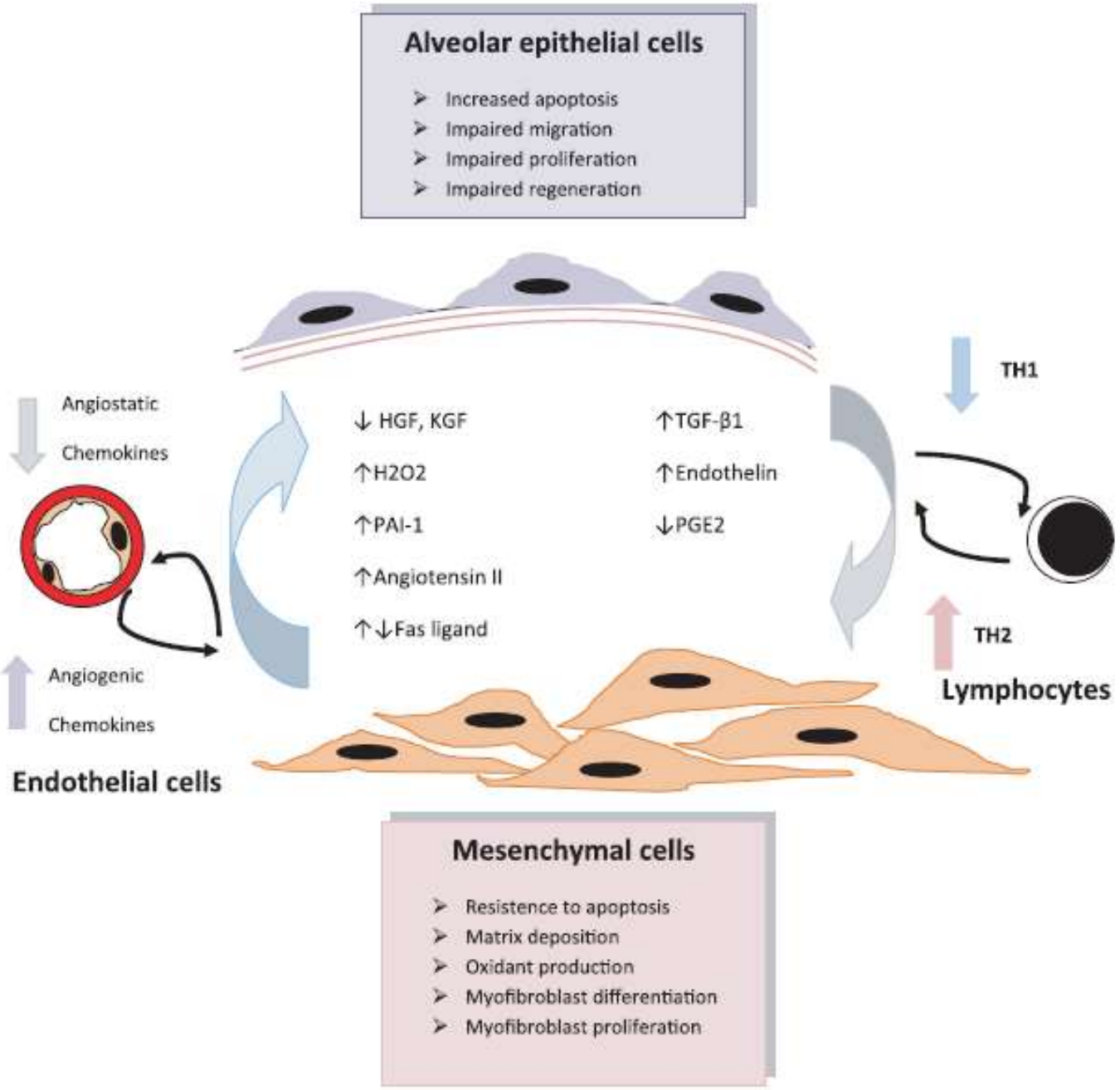
Pathogenesis

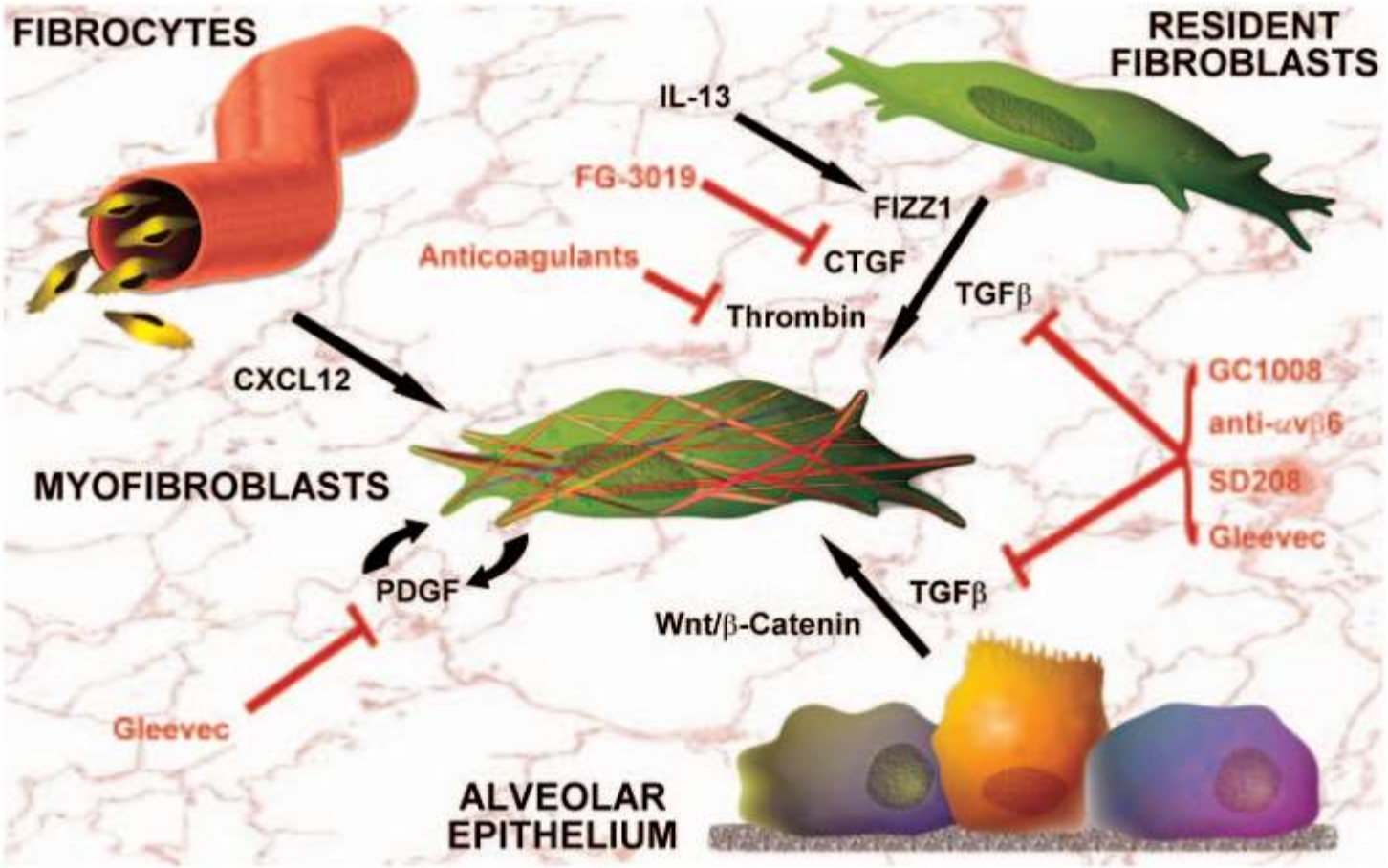
- Although a disease of unknown etiology, the current hypothesis regarding its development conceptualizes ongoing multiple, small, focal, and isolated episodes of epithelial injury followed by a pathologic fibrotic-repair mechanism

IPF new insight on to pathogenesis and treatment.
Allergy 2010,65:537-553



IPF new insight on to pathogenesis and treatment.
Allergy 2010,65:537-553


Alveolar epithelial cells
Increased apoptosis
Impaired migration
Impaired proliferation
Impaired regeneration
Angiostatic
Chemokines
↓ HGF, KGF
↑H2O2
↑PAI-1
↑Angiotensin II
↑↓Fas ligand
↑TGF-β1
↑Endothelin
↓PGE2
TH1
TH2
Lymphocytes
Angiogenic
Chemokines
Endothelial cells
Mesenchymal cells
Resistence to apoptosis
Matrix deposition
Oxidant production
Myofibroblast differentiation
Myofibroblast proliferation



Molecular targets in pulmonary fibrosis.
Chest 2007;132:1311-131

Agent: antiinflammatory/ immunosuppressant	
Corticosteroids	Immunosuppressant and antiinflammatory
Cyclophosphamide	Alkylating agent with antiinflammatory properties
Azathioprine	Inhibits adenine deaminase and impairs cell proliferation (particularly leukocytes); antiinflammatory
Etanercept	Soluble recombinant tumor necrosis factor-α receptor that inhibits tumor necrosis factor-α; antiinflammatory and antifibrotic
Platelet-activating factor receptor antagonists (WEB 2086)	PAF is a potent proinflammatory mediator that can lead to secretion of eicosanoids, TNF-α, IL-1β, as well as affecting vascular permeability and alveolitis[71]

Molecular targets in pulmonary fibrosis.
Chest 2007;132:1311-131

Agent: antifibrotic and/or antiangiogenic		
GC1008 (anti–TGF-β1, TGF-β2, and TGF-β3)	Monoclonal antibodies that neutralize TGF-β1, TGF-β2, and TGF-β3; antifibrotic	Phase I study ongoing (Genzyme and Cambridge Antibody Technology)
Anti-$\alpha v\beta_6$ integrin	$\alpha v\beta_6$ blocking antibodies or antagonists could block TGF-β activation; antifibrotic	Preclinical trials ongoing (Biogen)
SD-208 (ALK-5 kinase inhibitor)	Small-molecule TGF-β receptor kinase inhibitor; antifibrotic	
Decorin	Binds to and inhibits TGF-β activity; antifibrotic	
Pirfenidone	Antifibrotic and antioxidant properties; inhibits fibroblast/myofibroblast function	Azuma et al[73]/2005; also CAPACITY phase III trials are currently enrolling patients (InterMune)
Imatinib mesylate	Tyrosine kinase inhibitor that blocks both the PDGF receptor and c-Abl (downstream of TGF-β2); antifibrotic	Phase II/III trial completed (Novartis)

Molecular targets in pulmonary fibrosis.
Chest 2007;132:1311-131

TABLE 1 Completed clinical trials in idiopathic pulmonary fibrosis

	Drug	Mechanism of Action
IFIGENIA [20]	NAC	Antioxidant
PANTHER-IPF [21]	Prednisone	Antioxidant
	Azathioprine	Immunosuppression
	NAC	
Taniguchi [22]	Pirfenidone	Antifibrotic
CAPACITY 1 [23]	Pirfenidone	Antifibrotic
CAPACITY 2 [23]	Pirfenidone	Antifibrotic
ACE-IPF [24]	Warfarin	Anticoagulant
TOMORROW [25]	BIBF 1120	Tyrosine-kinase inhibitor
Daniels [26]	Imatinib mesylate	Tyrosine-kinase inhibitor
STEP-IPF [27]	Sildenafil	Phosphodiesterase-5 inhibitor
BUILD-1 [28]	Bosentan	Endothelin-receptor antagonist
BUILD-3 [29]	Bosentan	Endothelin-receptor antagonist
ARTEMIS-IPF [30]	Ambrisentan	Endothelin-receptor antagonist
MUSIC-IPF [31]	Macitentan	Endothelin-receptor antagonist
Raghu [32]	IFN-γ	Immunomodulation
INSPIRE [33]	IFN-γ	Immunomodulation

Pharmacological treatment of IPF from past to future . Eu Resp Rev.2013;22:281-291

PIRFENIDONE

- Orally administered pyridine
- Antiinflammatory, antifibrotic, antioxidant properties
- TGF-β antagonism
- Also acts as antifibrotic by:
  - directly altering the expression, synthesis, and accumulation of collagen
  - Inhibiting recruitment, proliferation and expression of extracellular matrix-producing cells
  - Inhibits fibroblast/myofibroblast function

Double-blind, Placebo-controlled Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Arata Azuma, Toshihiro Nukiwa, Eiyasu Tsuboi, Moritaka Suga, Shosaku Abe, Koichiro Nakata, Yoshio Taguchi, Sonoko Nagai, Harumi Itoh, Motoharu Ohi, Atsuhiko Sato, and Shoji Kudoh for the members of the Research Group for Diffuse Lung Diseases in Japan; and Ganesh Raghu

Am J Respir Crit Care Med Vol 171. pp 1040–1047, 2005

107 patients: Placebo vs Pirfenidone 1800 mg/d

Only mild-moderate: Resting pO2 > 70 mmHg

- Difference in change in lowest oxygen saturation by SpO2 during a 6MWT after 6 months was not significant (p 0.0722)
- In subset of patients who maintained a SpO2 greater than 80% during a 6MWT, the lowest SpO2 improved during a 6MWT in pirfenidone group at 6 and 9months (p0.0069 and 0.0305).
- Positive treatment effect was demonstrated in secondary endpoints:

  (1) change in VC measurements at 9 months (p 0.0366)

  (2) episodes of acute exacerbation of IPF occurring exclusively in the placebo group during the 9 months (p 0.0031)
- Significant adverse events were associated with pirfenidone; however, adherence to treatment regimen was similar between pirfenidone and placebo groups.

Eur Respir J 2010; 35: 821–829
DOI: 10.1183/09031936.00005209

Pirfenidone in idiopathic pulmonary fibrosis

H. Taniguchi*, M. Ebina#, Y. Kondoh*, T. Ogura¶, A. Azuma+, M. Suga§, Y. Taguchi^f, H. Takahashi**, K. Nakata##, A. Sato¶¶, M. Takeuchi++, G. Raghu§§, S. Kudoh+ and T. Nukiwa#, and the Pirfenidone Clinical Study Group in Japan^ff

Primary end point

change in FVC from baseline to 52 weeks

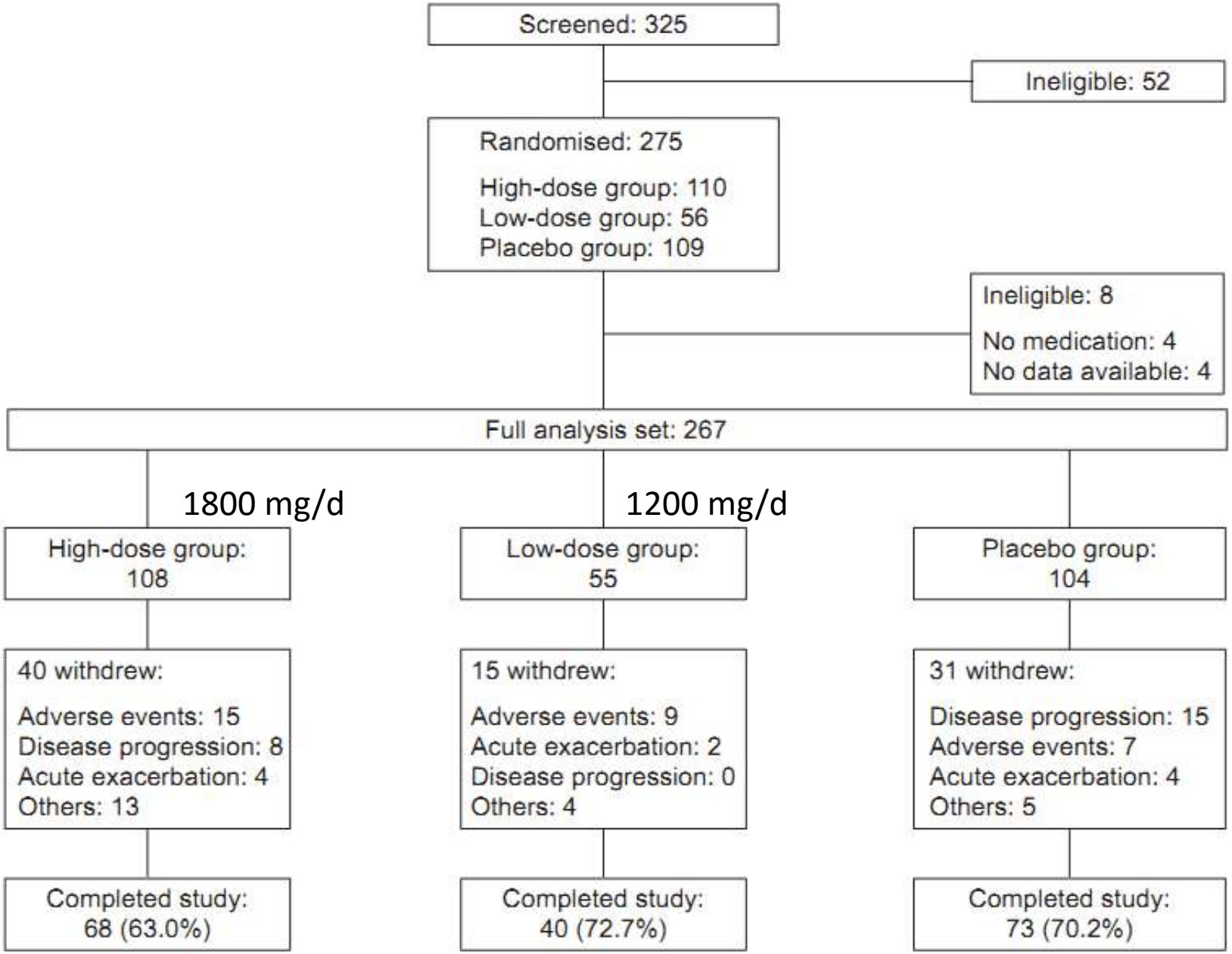
Seconary end point

Progression free survival and change in lowest spo2 during 6MWT

Inclusion/Exclusion

- Inclusion: Adults with IPF with following
  1) oxygen desaturation of >5% difference between resting SpO2 and the lowest SpO2 during a 6MWT
  2) **the lowest SpO2 during the 6MET of >85% on room air.**

- Exclusion criteria:
  1) decrease in symptoms during preceding 6 months
  2) use of immunosuppressants and/or oral steroids >10 mg/day during preceding 3 months
  3) clinical features of IIP other than IPF
  4) evidence of known coexisting pulmonary hypertension, asthma, tuberculosis, bronchiectasis, aspergillosis or severe respiratory infection.


Screened: 325
Ineligible: 52
Randomised: 275
High-dose group: 110
Low-dose group: 56
Placebo group: 109
Ineligible: 8
No medication: 4
No data available: 4
Full analysis set: 267
1800 mg/d
1200 mg/d
High-dose group: 108
Low-dose group: 55
Placebo group: 104
40 withdrew:
Adverse events: 15
Disease progression: 8
Acute exacerbation: 4
Others: 13
15 withdrew:
Adverse events: 9
Acute exacerbation: 2
Disease progression: 0
Others: 4
31 withdrew:
Disease progression: 15
Adverse events: 7
Acute exacerbation: 4
Others: 5
Completed study: 68 (63.0%)
Completed study: 40 (72.7%)
Completed study: 73 (70.2%)

Subjects	108	55	104	
Male	85 (78.7)	47 (85.5)	81 (77.9)	0.53
Female	23 (21.3)	8 (14.5)	23 (22.1)	
Age yrs	65.4±6.2	63.9±7.5	64.7±7.3	0.44
Smoking history				
Smokers	5 (4.6)	10 (18.2)	13 (12.5)	0.07[#]
Ex-smokers	81 (75.0)	33 (60.0)	70 (67.3)	
Never smokers	22 (20.4)	12 (21.8)	21 (20.2)	
Time since first diagnosis yrs				
<1	38 (35.2)	20 (36.4)	41 (39.4)	0.86
1–3	29 (26.9)	13 (23.6)	25 (24.0)	
⩾3	41 (38.0)	22 (40.0)	38 (36.5)	
Prior treatment (steroids) received				
No	99 (91.7)	49 (89.1)	98 (94.2)	0.49
Yes	9 (8.3)	6 (10.9)	6 (5.8)	
Current steroid use	8 (7.4)	6 (10.9)	5 (4.8)	
Surgical lung biopsy	26 (24.1)	16 (29.1)	28 (26.9)	0.78
VC mL	2400.8±638.4	2437.8±684.8	2472.3±698.9	0.74
VC % pred	77.3±16.8	76.2±18.7	79.1±17.4	0.57
TLC % pred	73.2±16.5	72.4±15.6	75.2±15.7	0.50
$D_{L,CO}$ % pred	52.1±16.8	53.6±19.1	55.2±18.2	0.44
P_{a,O_2} at rest mmHg	79.8±10.2	81.6±8.4	81.0±9.5	0.48
P_{A-a,O_2} mmHg	18.4±11.3	16.9±9.6	17.4±9.7	0.64
Lowest S_{p,O_2} %	89.0±2.3	88.8±2.4	89.0±2.0	0.86
Presence of desaturation below 88% on walk test	34 (31.5)	19 (34.5)	24 (23.1)	

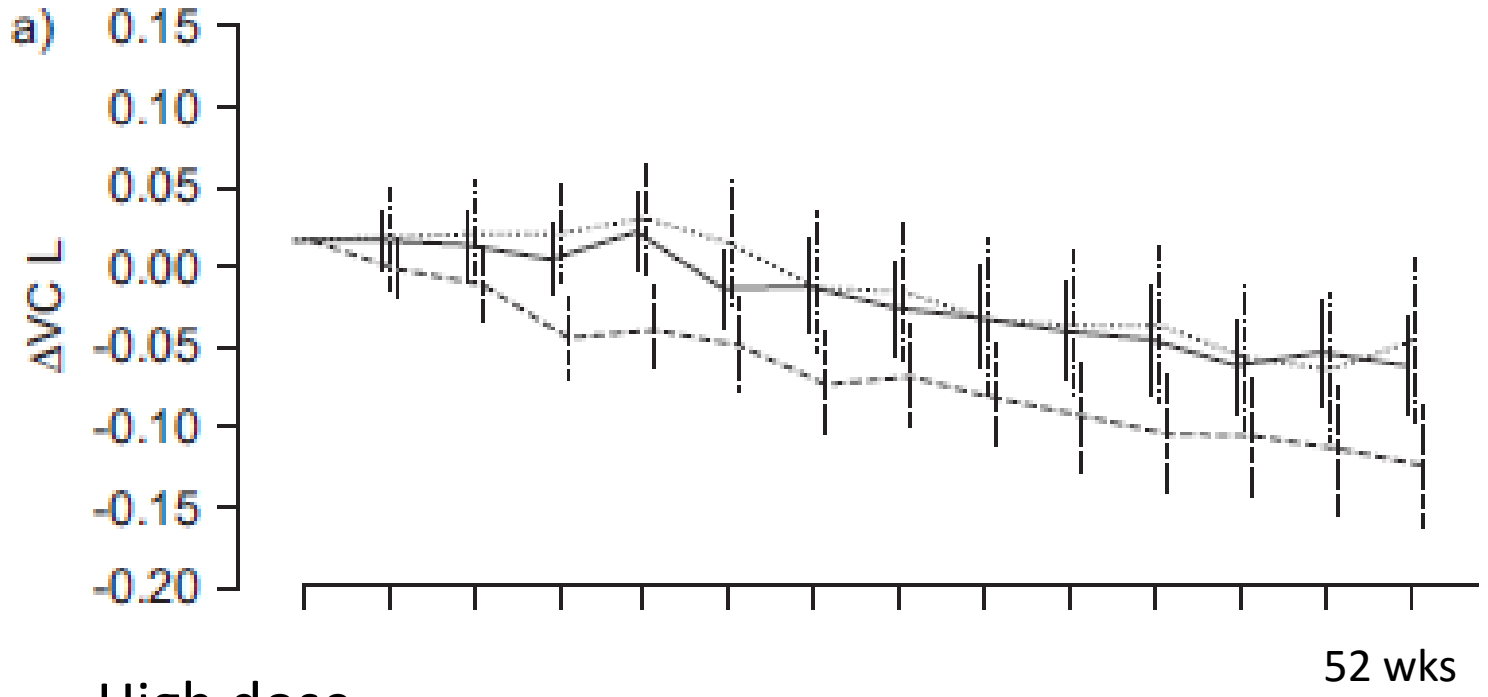
Data are presented as n, n (%) or mean±SD, unless stated otherwise. VC: vital capacity; % pred: % predicted; TLC: total lung capacity; $D_{L,CO}$: diffusion capacity of the lung for carbon monoxide; P_{a,O_2}: arterial oxygen tension; P_{A-a,O_2}: alveolar–arterial oxygen tension difference; S_{p,O_2}: oxygen saturation measured by pulse oximetry,

TABLE 3 Comparison of changes in vital capacity

	Crude mean ± SD				Comparison of adjusted means based on ANCOVA[#]			
	Baseline L	Subjects n	52 weeks L	Subjects n	Subjects n	Adjusted mean ± SE	Difference from placebo mean ± SE L	p-value
High dose	2.40 ± 0.64	106	2.36 ± 0.73	67	104	-0.09 ± 0.02	0.07 ± 0.03	0.0416
Low dose	2.44 ± 0.68	55	2.34 ± 0.71	38	54	-0.08 ± 0.03	0.09 ± 0.04	0.0394
Placebo	2.47 ± 0.70	104	2.42 ± 0.75	72	103	-0.16 ± 0.02		

[#]: negative and positive of the changes represent deterioration and improvement from baseline, respectively. Covariates: baseline vital capacity.

FVC on Follow up



——— High dose

…… Low dose

------ Placebo

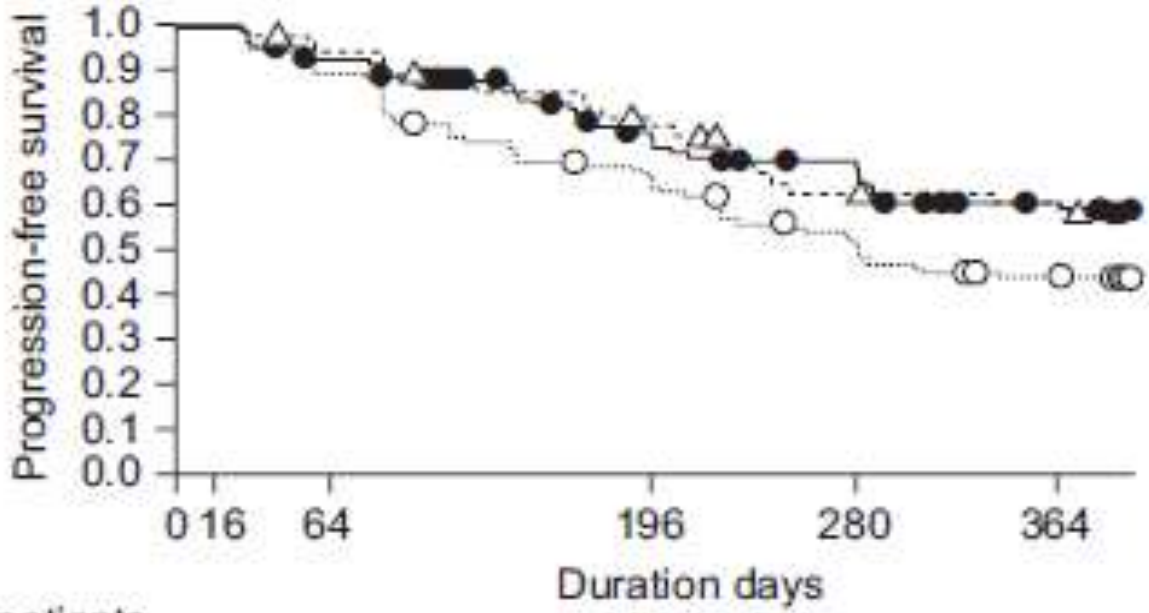


FIGURE 4. Kaplan–Meier plot of progression-free survival time among idiopathic pulmonary fibrosis patient groups. —: high dose; – –: low dose; ·····: placebo. Symbols on the curve represent the censored points where patients discontinued the study treatment due to causes other than progression of the disease. Kaplan–Meier curves were compared with the log-rank test: p=0.0280 between the high-dose group and placebo group; p=0.0655 between the low-dose group and placebo group; p=0.9106 between the high-dose group and low-dose group.

- No significant difference found in:
  - TLC
  - DLCO
  - Lowest SpO2 on 6 MWT
  - Serum markers

Adverse event	High dose	Low dose	Placebo	p-value[¶]		
				High dose *versus* placebo	Low dose *versus* placebo	High dose *versus* low dose
Subjects	109	55	107			
Any adverse event	109 (100.0)	54 (98.2)	106 (99.1)	0.50	1.00	0.34
Photosensitivity	56 (51.4)	29 (52.7)	24 (22.4)	<0.01	<0.01	1.00
Eczema asteatotic	0 (0.0)	3 (5.5)	0 (0.0)		0.04	0.04
Anorexia	18 (16.5)	6 (10.9)	3 (2.8)	<0.01	0.06	0.48
Abdominal discomfort	3 (2.8)	4 (7.3)	0 (0.0)	0.25	0.01	0.23
Dizziness	8 (7.3)	0 (0.0)	1 (0.9)	0.04	1.00	0.05
Nasopharyngitis	54 (49.5)	30 (54.5)	70 (65.4)	0.02	0.23	0.62
Upper respiratory tract infection	1 (0.9)	3 (5.5)	9 (8.4)	<0.01	0.75	0.11
γ-GTP elevation	25 (22.9)	12 (21.8)	10 (9.3)	<0.01	0.05	1.00
WBC decrease	4 (3.7)	3 (5.5)	0 (0.0)	0.12	0.04	0.69

Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials

Paul W Noble, Carlo Albera, Williamson Z Bradford, Ulrich Costabel, Marilyn K Glassberg, David Kardatzke, Talmadge E King Jr, Lisa Lancaster, Steven A Sahn, Javier Szwarcberg, Dominique Valeyre, Roland M du Bois, for the CAPACITY Study Group

CAPACITY TRIALS

(Clinical studies assessing Pirfenidone in IPF : Research of efficacy and safety outcomes)

Lancet 2011;377:1760-1769

Inclusion criteria – CAPACITY TRIAL

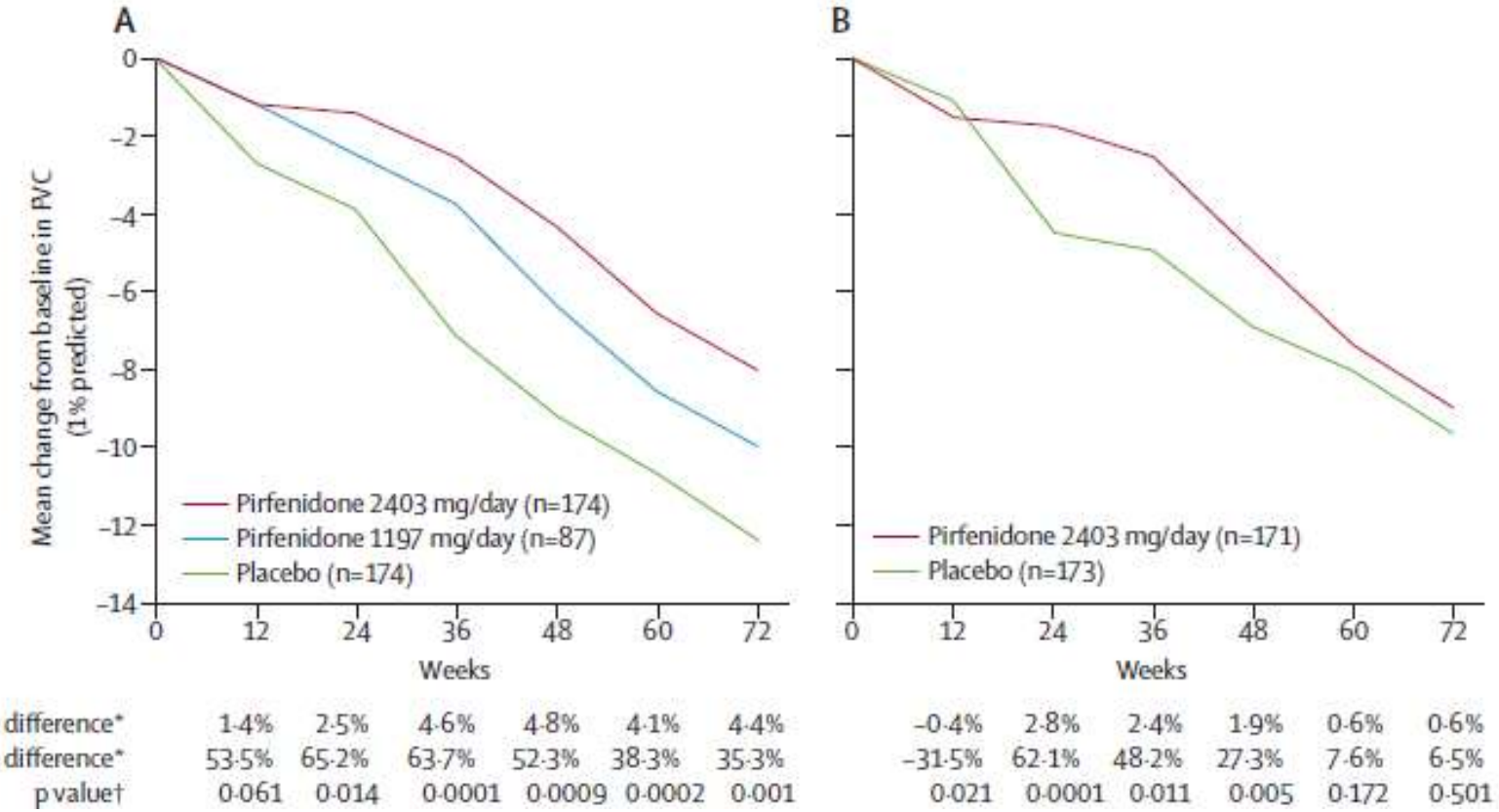
- Age 40-80yrs with IPF diagnosis
- Predicted FVC atleast 50%
- Predicted Dlco atlest 35%
- Either predicted FVC or Dlco < 90% with 6MWD of atleast 150m

Mild to moderate lung function

	Study 004			Study 006	
	Pirfenidone 1197 mg/day (n=87)	Pirfenidone 2403 mg/day (n=174)	Placebo (n=174)	Pirfenidone 2403 mg/day (n=171)	Placebo (n=173)
Age (years)	68·0 (7·6)	65·7 (8·2)	66·3 (7·5)	66·8 (7·9)	67·0 (7·8)
Men	65 (75%)	118 (68%)	128 (74%)	123 (72%)	124 (72%)
White	83 (95%)	168 (97%)	168 (97%)	169 (99%)	171 (99%)
Weight (kg)					
Men	88·4 (13·5)	91·3 (15·9)	88·9 (16·1)	95·4 (17·4)	93·2 (15·1)
Women	72·8 (13·0)	77·0 (13·2)	77·0 (13·6)	76·6 (14·0)	77·5 (14·8)
Non-US enrolment	29 (33%)	60 (34%)	60 (34%)	23 (13%)	23 (13%)
Smoking status					
Never	27 (31%)	56 (32%)	51 (29%)	59 (35%)	64 (37%)
Former	57 (66%)	110 (63%)	114 (66%)	112 (65%)	101 (58%)
Current	3 (3%)	8 (5%)	9 (5%)	0	8 (5%)
Definite idiopathic pulmonary fibrosis (HRCT)	83 (95%)	159 (91%)	164 (94%)	149 (87%)	158 (91%)
Surgical lung biopsy	32 (37%)	86 (49%)	85 (49%)	94 (55%)	94 (54%)
Diagnosis (≤1 year) of idiopathic pulmonary fibrosis	46 (53%)	83 (48%)	81 (47%)	100 (58%)	107 (62%)
Predicted FVC (%)	76·4 (14·4)	74·5 (14·5)	76·2 (15·5)	74·9 (13·2)	73·1 (14·2)
DLco (% predicted)	47·2 (8·2)	46·4 (9·5)	46·1 (10·2)	47·8 (9·8)	47·4 (9·2)
A-a gradient (mm Hg)	15·5 (10·4)	17·7 (10·6)	18·9 (14·7)	18·3 (11·1)	17·0 (10·4)
6MWT distance (m)	417·5 (112·8)	411·1 (91·8)	410·0 (90·9)	378·0 (82·2)	399·1 (89·7)
Use of supplemental oxygen	15 (17%)	29 (17%)	25 (14%)	48 (28%)	49 (28%)

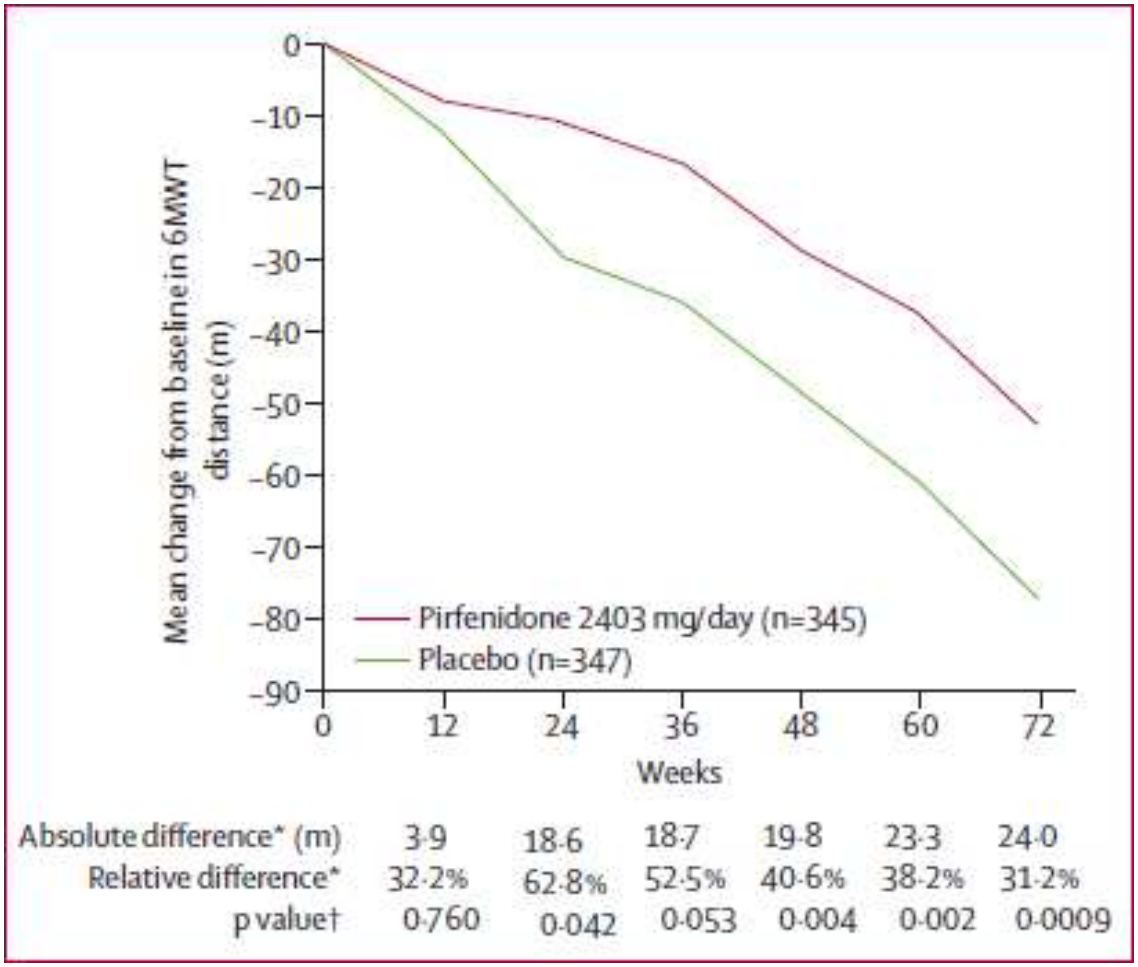
	Study 004				Study 006				Pooled data			
	Pirfenidone 2403 mg/day (n=174)	Placebo (n=174)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=171)	Placebo (n=173)	Absolute difference (95% CI)	p value*	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)	Absolute difference (95% CI)	p value*
Categorical change in FVC ≥10%	35 (20%)	60 (35%)	14·4 (7·4 to 21·3)	0·001†	39 (23%)	46 (27%)	3·8 (−2·7 to 10·2)	0·440†	74 (21%)	106 (31%)	9·1 (4·3 to 13·9)	0·003†
Progression-free survival time‡	..	..	0·64 (0·44 to 0·95)	0·023§	..	..	0·84 (0·58 to 1·22)	0·355§	..	..	0·74 (0·57 to 0·96)	0·025§
Mean change in 6MWT distance (m)	−60·4	−76·8	16·4 (−10·9 to 43·7)	0·171	−45·1	−76·9	31·8 (3·2 to 60·4)	0·0009	−52·8	−76·8	24·0 (4·3 to 43·7)	0·0009
Mean change in DLco (% predicted)	−7·9	−9·9	2·0 (−0·4 to 4·4)	0·145	−9·8	−9·2	−0·5 (−3·2 to 2·2)	0·996	−8·8	−9·6	0·7 (−1·1 to 2·5)	0·301
Mean change in dyspnoea score¶	12·1	15·2	−3·1 (−8·5 to 2·3)	0·509	11·9	13·9	−2·0 (−7·6 to 3·6)	0·604	12·0	14·5	−2·5 (−6·4 to 1·4)	0·405
Mean change in worst SpO_2 during 6MWT (%)	−1·5	−2·3	0·8 (−0·2 to 1·8)	0·087	−1·9	−1·3	−0·5 (−1·7 to 0·7)	0·893	−1·7	−1·8	0·1 (−0·7 to 0·9)	0·261
Time to worsening in idiopathic pulmonary fibrosis	..	..	0·84 (0·50 to 1·42)‡	0·515§	..	..	0·73 (0·43 to 1·24)‡	0·248§	..	..	0·78 (0·54 to 1·14)‡	0·201§
Categorical change in HRCT-diagnosed fibrosis‖	NA	NA	NA	NA	NA	NA	NA	0·894	NA	NA	NA	NA

FVC on Follow-up



Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%	−0·4%	2·8%	2·4%	1·9%	0·6%	0·6%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%	−31·5%	62·1%	48·2%	27·3%	7·6%	6·5%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001	0·021	0·0001	0·011	0·005	0·172	0·501

6MWT on follow-up



Absolute difference* (m)	3·9	18·6	18·7	19·8	23·3	24·0
Relative difference*	32·2%	62·8%	52·5%	40·6%	38·2%	31·2%
p value†	0·760	0·042	0·053	0·004	0·002	0·0009

Mortality

	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)	Hazard ratio* (95% CI)	p value†
Overall				
All-cause mortality	27 (8%)	34 (10%)	0·77 (0·47–1·28)	0·315
Idiopathic-pulmonary-fibrosis-related mortality‡	18 (5%)	28 (8%)	0·62 (0·35–1·13)	0·117
On-treatment§				
All-cause mortality	19 (6%)	29 (8%)	0·65 (0·36–1·16)	0·141
Idiopathic-pulmonary-fibrosis-related mortality‡	12 (3%)	25 (7%)	0·48 (0·24–0·95)	0·030

Data are number (%). *Based on the Cox-proportional hazard model. †Log-rank test (pirfenidone 2403 mg/day *vs* placebo). ‡Assessed by the investigator, who remained masked to treatment assignment. §Defined as the time from randomisation until 28 days after the last dose of study drug.

***Table 3*: All-cause and idiopathic-pulmonary-fibrosis-related mortality in the pooled population**

	Pirfenidone 2403 mg/day (n=345)	Placebo (n=347)
Nausea	125 (36%)	60 (17%)
Rash	111 (32%)	40 (12%)
Dyspepsia	66 (19%)	26 (7%)
Dizziness	63 (18%)	35 (10%)
Vomiting	47 (14%)	15 (4%)
Photosensitivity reaction	42 (12%)	6 (2%)
Anorexia	37 (11%)	13 (4%)
Arthralgia	36 (10%)	24 (7%)
Insomnia	34 (10%)	23 (7%)
Abdominal distension	33 (10%)	20 (6%)
Decreased appetite	30 (9%)	10 (3%)
Stomach discomfort	29 (8%)	6 (2%)
Weight reduction	28 (8%)	12 (3%)
Abdominal pain	26 (8%)	12 (3%)
Asthenia	24 (7%)	13 (4%)
Pharyngolaryngeal pain	24 (7%)	16 (5%)
Pruritus	22 (6%)	14 (4%)
Hot flush	18 (5%)	4 (1%)

Data are number of patients (%). *Occurring in 5% or more of patients given pirfenidone 2403 mg/day in study 004 and study 006, and with an incidence 1-5 times greater than that in patients given placebo.

Table 4: **Treatment-emergent adverse events***

Respiratory Medicine (2013) 107, 1431–1437

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Safety and efficacy of pirfenidone in idiopathic pulmonary fibrosis in clinical practice

Ryo Okuda*, Eri Hagiwara, Tomohisa Baba, Hideya Kitamura, Terufumi Kato, Takashi Ogura

Department of Respiratory Medicine, Kanagawa Cardiovascular and Respiratory Center, 6-16-1 Tomioka-higashi, Kanazawa-ku, 236-0051 Yokohama, Japan

Received 10 February 2013; accepted 13 June 2013

Materials and method

- Study design : retrospective cohort study
- Sample size : 76
- Study period: Dec 1, 2008 to Mar 31,2011
- Study Place : Yokohama , Japan
- Pirfenidone dose was escalated over 28 days to 1800mg.
- All patients – safety and efficacy analysis

Baseline characteristics

Subject	76
Male	60
Female	16
Age (yrs)	70.5±8.3
Smoking History	
Never smoker	16
Ex and current smoker	60
Brinkman index	849±637
Surgical lung biopsy	
Yes	36
No	40
IPF ATS/ERS statement	
IPF	66
Probable IPF	2
Possible IPF	8

Baseline characteristics

Prior Treatment Received	
No	59
Yes	17
Steroids only	7
Steroids + immunosupressant	10
Immunosupressant only	0
Average dose of prednisolone(mg/day)	7.8± .5
Combined treatment received with pirfenidone	
No	44
Yes	32
Steroids only	19
Steroids+ immunosupressant	13
Immunosupressant only	0
Average dose of Prednisolone (mg/day)	9.6±3.4

Baseline characteristics

Disease severity	
Japanese classification	76
Stage I	20
Stage II	11
Stage III	15
Stage IV	27
Unmeasurable	3

Disease severity	
USA criteria	76
Mild	11
Moderate	38
Severe	11
Unmeasurable	17

Baseline characteristics

Blood tests	
KL-6 (U/ml) (152-400 U/mL)	1428±1129
SP-D(ng/ml) (0-109.9 ng/mL)	323± 280
PaO2 (Torr)	76±11.9
Pulmonary function	
VC(L)	2.05±0.61
VC % Predicted	66.5±15.8
FVC(L)	2.04±0.61
FVC% pred	65.3±16.1
FEV1(L)	1.67±0.48
Dlco % Pred	55.9±17.8
6MWT	
Distance (m)	313±105
Lowest Spo2	86±5.5%

Results

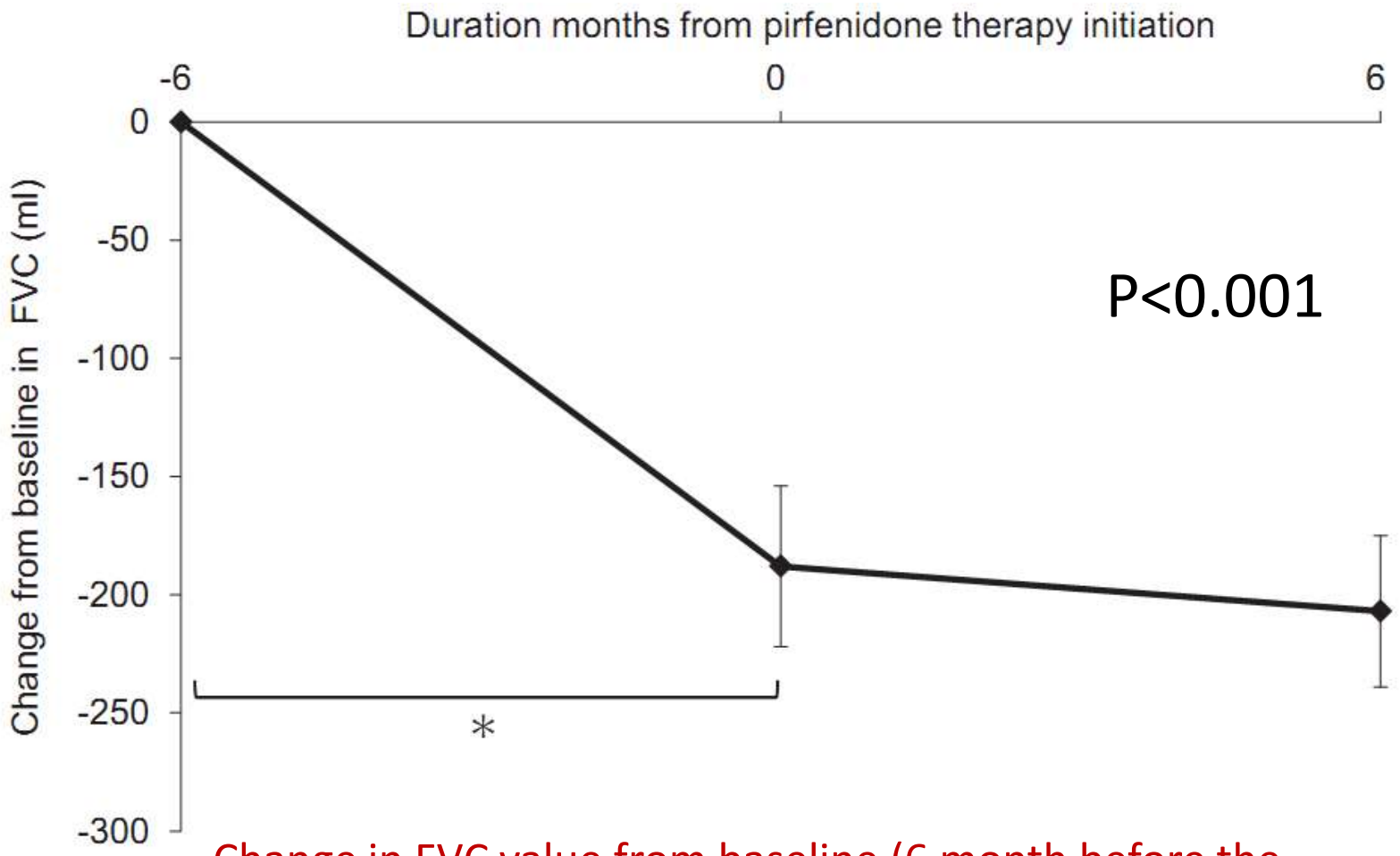
Safety :

- Discontinued – 34.2%
- Discontinued due to adverse effects – 18.4%
- Anorexia - 42% which improved after dose reduction in 84%
- Mean time of anorexia – 90 days
- No correlelation between anorexia and severity of IPF / steroid or immunosupression intake

Adverse Events

	Grade					
	Total	1	2	3	4–5	Onset of events
Adverse events	64 (84.2)					(days)
Photosensitivity	14 (18.4)	9	5	0	0	116 ± 63
Anorexia	32 (42.1)	23	7	2	0	96 ± 97
Nausea	9 (11.8)	7	2	0	0	145 ± 135
Gastric distress	9 (11.8)	9	0	0	0	83 ± 95
Fatigue	11 (14.5)	6	5	0	0	114 ± 107
Drowsiness	5 (6.6)	5	0	0	0	80 ± 94
Rash	5 (6.6)	5	0	0	0	134 ± 75
Hepatic dysfunction						
γ-GTP elevation	17 (22.4)	13	4	0	0	128 ± 83
AST elevation	13 (17.1)	12	0	1	0	93 ± 80
ALT elevation	14 (18.4)	13	0	1	0	119 ± 96
Others	4 (5.3)	4	0	0	0	

FVC N=36



P<0.001

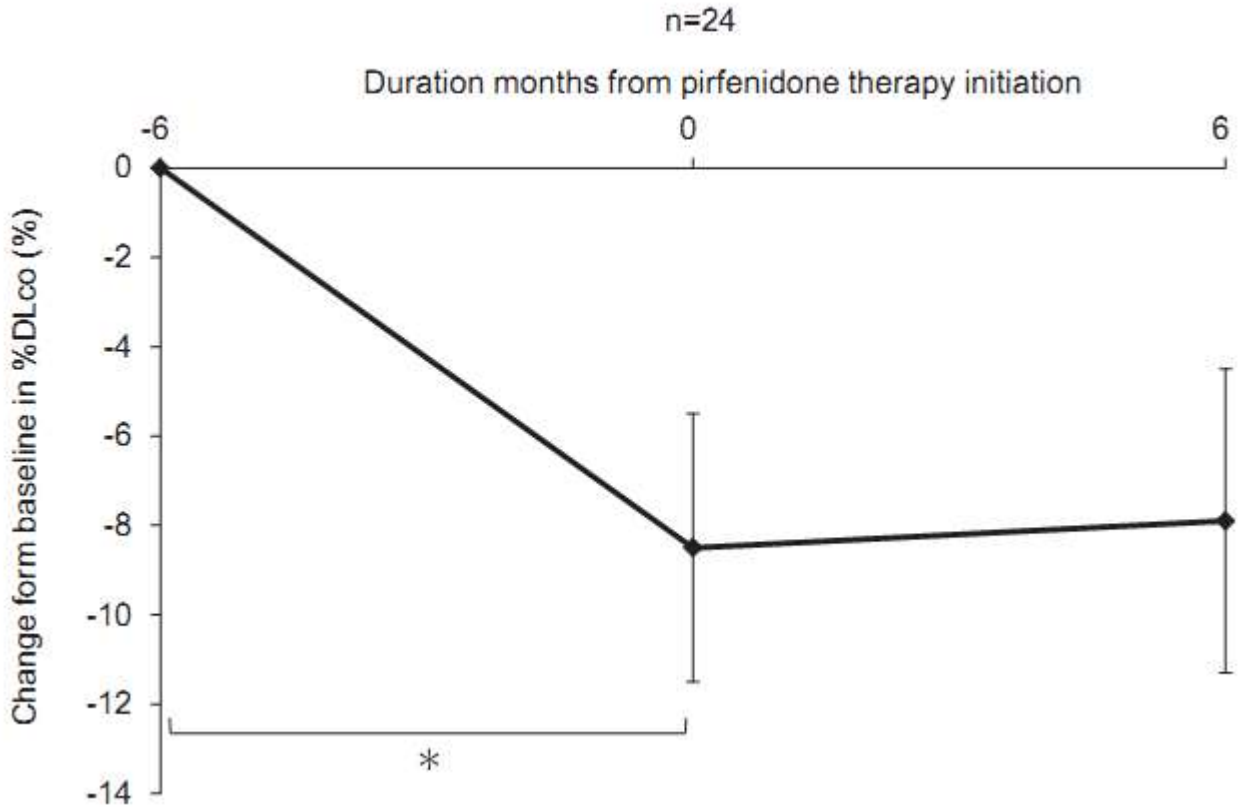
Change in FVC value from baseline (6 month before the initiation of therapy) was -188ml at the initiation of pirfenidone therapy and -207 ml after 6 months of therapy

Table 4 FVC decline in subpopulations characterized by %FVC and by change in FVC before therapy.

%FVC at initiation of therapy	*n*	Mean change in FVC for 6 months before therapy (ml)	Mean change in FVC for 6 months after therapy (ml)	*p*-Value
%FVC ≥80	4	−60 ± 96	−80 ± 69	0.840
80> %FVC ≥70	11	−130 ± 58	20 ± 70	0.282
70> %FVC ≥60	10	−210 ± 44	−60 ± 63	0.156
60> %FVC	11	−280 ± 72	−80 ± 55	0.074
Decline in FVC for 6 months before therapy	***n***	**Mean change in FVC for 6 months before therapy (ml)**	**Mean change in FVC for 6 months after therapy (ml)**	***p*-Value**
≥150 ml	16	−350 ± 48	30 ± 58	<0.001
<150 mL	20	−60 ± 20	−100 ± 31	0.274

Paired *t*-test was performed. Values are given as mean ± standard error.

DLco



P<0.05

Change in %DLco from baseline (6 month before initiation of pirfenidone therapy) was -8.5% ±3%at initiation of therapy and -7.9%±3.4 after 6 months of Pirfenidone therapy.

KL-6 & SP-D

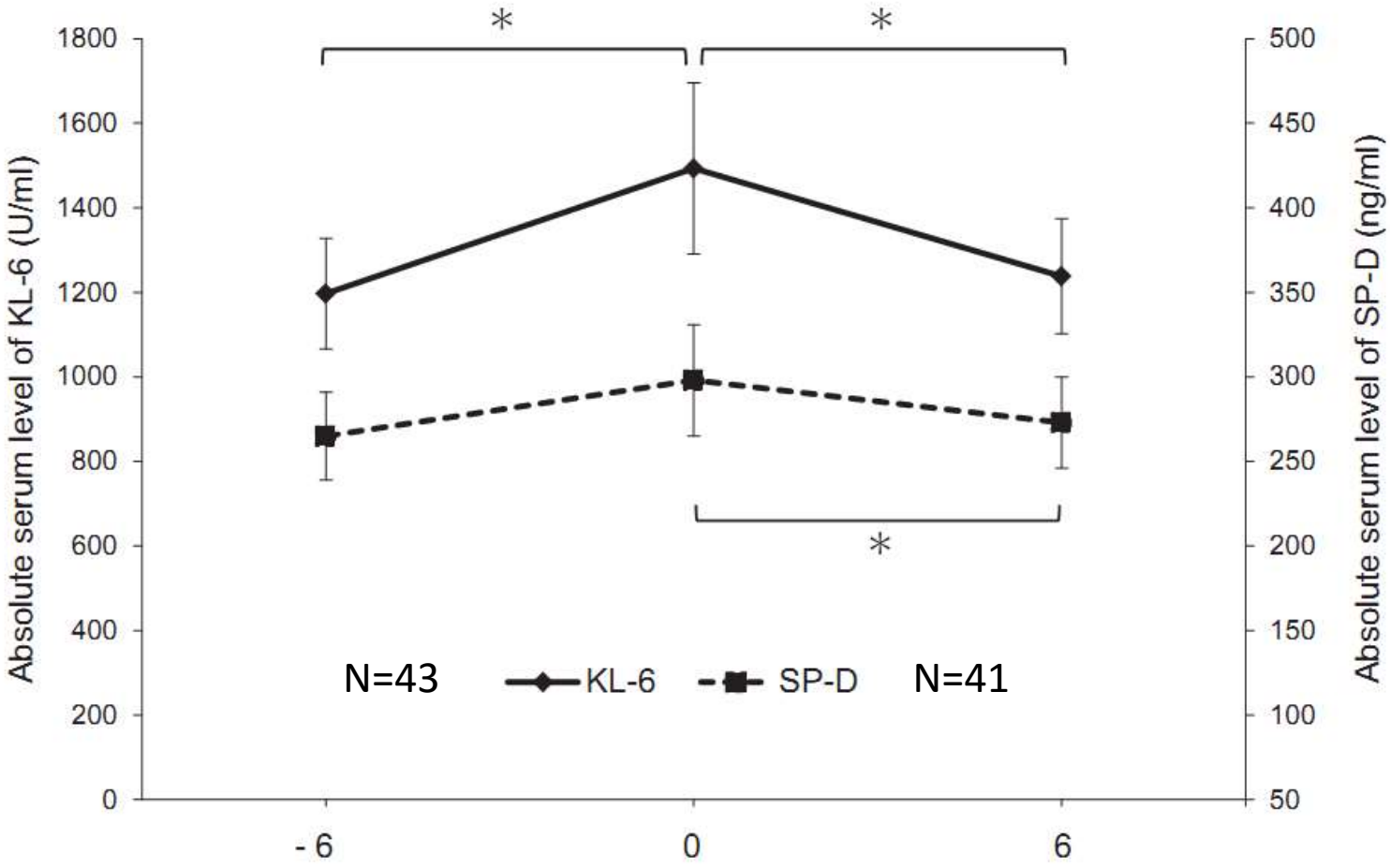

*
*
*
1800
1600
1400
1200
1000
800
600
400
200
0
500
450
400
350
300
250
200
150
100
50
Absolute serum level of KL-6 (U/ml)
Absolute serum level of SP-D (ng/ml)
N=43
KL-6
SP-D
N=41
- 6
0
6

Table 6 Comparison of 6-min walk test results.

6MWT					
	n	Initiation of therapy	*n*	6 months after therapy	*p*-Value
Mini SpO_2 (%)	33	86 ± 1	20	88 ± 1	0.399
Distance (m)	29	342 ± 21	13	383 ± 32	0.143

6MWT: 6-min walk test; SpO_2: oxygen saturation measured by pulse oximetry. Data are presented as mean ± standard error.

Acute exacerbations 4(76) – 5.3% , 2 patient died due to acute exacerbation.

Pirfenidone - Conclusion

- Pirfenidone attenuates the FVC decline
- Also improv Progression free survival and exercise capacity
- Anorexia common side effect – but no correlation with disease severity
- Others - Photosensitivity, Hepatotoxicity
- In case of side effects dose modification should be tried rather stopping since low dose also has a beneficial effect in lung function

- The effect of therapy more pronounced in the group with faster decline of FVC
- Serum levels interstitial pneumonia markers showed statistically significant decrease after therapy

N-Acetyl cysteine

- An oxidant–antioxidant imbalance may contribute to the disease process in IPF
- Acetylcysteine, a precursor of the major antioxidant glutathione, given at a daily dose of 1800 mg, has been shown to restore depleted pulmonary glutathione levels

Antioxidative and Clinical Effects of High-dose *N*-Acetylcysteine in Fibrosing Alveolitis

Adjunctive Therapy to Maintenance Immunosuppression

JÜRGEN BEHR, KONRAD MAIER, BARBARA DEGENKOLB, FRITZ KROMBACH, and CLAUS VOGELMEIER

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Acetylcysteine in Idiopathic Pulmonary Fibrosis

Maurits Demedts, M.D., Juergen Behr, M.D., Roland Buhl, M.D., Ulrich Costabel, M.D., P.N., Richard Dekhuijzen, M.D., Henk M. Jansen, M.D., William MacNee, M.D., Michiel Thomeer, M.D., Benoit Wallaert, M.D., François Laurent, M.D., Andrew G. Nicholson, M.D., Eric K. Verbeken, M.D., Johny Verschakelen, M.D., Christopher D.R. Flower, M.D., Frédérique Capron, M.D., Stefano Petruzzelli, M.D., Paul De Vuyst, M.D., Jules M.M. van den Bosch, M.D., Eulogio Rodriguez-Becerra, M.D., Giuseppina Corvasce, Ph.D., Ida Lankhorst, M.D., Marco Sardina, M.D., and Mauro Montanari, Ph.D., for the IFIGENIA Study Group*

Summary

- Double blinded multicentre RCT
- NAC 600 mg tds or placebo added to Azathioprine + Steroids
- 155 (80 NAC and 75 placebo) had UIP pattern and consented
- NAC slowed deterioration of VC and DLco at 12 months (P=0.02 and P=0.003 respectively).
- Mortality during the study was 9 percent among patients taking NAC and 11 percent among those taking placebo (P=0.69).
- No significant differences in type or severity of adverse events between patients taking acetylcysteine and those taking placebo, except for a significantly lower rate of myelotoxic effects in the group taking acetylcysteine (P=0.03)

Respiratory Research

BioMed Central

Research

Open Access

Lung function in idiopathic pulmonary fibrosis - extended analyses of the IFIGENIA trial

Jürgen Behr*[1], Maurits Demedts[2], Roland Buhl[3], Ulrich Costabel[4], Richard PN Dekhuijzen[5], Henk M Jansen[6], William MacNee[7], Michiel Thomeer[2], Benoit Wallaert[8], Francois Laurent[9], Andrew G Nicholson[10], Eric K Verbeken[2], Johny Verschakelen[2], CDR Flower[11], Stefano Petruzzelli[12], Paul De Vuyst[13], JMM van den Bosch[14], Eulogio Rodriguez-Becerra[15], Ida Lankhorst[16], Marco Sardina[16], Gabrielle Boissard[16] and the Ifigenia study group*

Summary

- Composite Physiologic Index (CPI) was calculated
- CPI uses the individual values for VC (% pred.), DLco (% pred.) and FEV1 (%pred.) to calculate the extent of fibrosis according to an empirically developed equation
- Effects of NAC on VC, DLco and CPI were significantly better if the baseline CPI was 50 points or lower (milder disease)

Aerosolised NAC

A pilot study of aerosolized N-acetylcysteine for idiopathic pulmonary fibrosis

Hiromi TOMIOKA[1,*], Youichirou KUWATA[2], Kazufumi IMANAKA[2], Kimio HASHIMOTO[3], Hisashi OHNISHI[1], Kimihide TADA[1], Hiroko SAKAMOTO[1], Hironobu IWASAKI[1]

Article first published online: 26 AUG 2005

DOI: 10.1111/j.1440-1843.2005.00725.x

Issue

Respirology

Volume 10, Issue 4, pages 449–455, September 2005

- 30 patients with IPF randomly assigned to one of the following inhalation therapies: NAC (352 mg per day) or bromhexine hydrochloride (4 mg per day) as the control
- Efficacy assessed by analysing changes occurring from baseline to 12 months in pulmonary function, the 6-min walking test, high-resolution CT, health-related quality of life, and serum KL-6-values.
- Significant differences between the N-acetylcysteine and control groups in terms of mean changes in lowest SaO_2 during the 6-min walking test ($P < 0.05$), serum KL-6 ($P < 0.05$), and the ground-glass score on high-resolution CT ($P < 0.01$). No significant differences were observed in pulmonary function, 6-min walking distance or quality of life.

Acetyl cysteine monotherapy?

- May be beneficial in improving lung function (VC) and gas exchange (Dlco) in patients with mild disease
- Concerns: Potential cost, low quality data, absence of ‘’no therapy’’ arm in the IFIGENIA study
- More data needed → PANTHER results awaited
- ATS/ERS Recommendation (weak): should not be used in majority

Triple Therapy (NAC+Aza+Prednisone)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prednisone, Azathioprine, and *N*-Acetylcysteine for Pulmonary Fibrosis

The Idiopathic Pulmonary Fibrosis Clinical Research Network*

No benefit – Increased mortality!

RESULTS

When approximately 50% of data had been collected (with 77 patients in the combination-therapy group and 78 in the placebo group), a planned interim analysis revealed that patients in the combination-therapy group, as compared with the placebo group, had an increased rate of death (8 vs. 1, P=0.01) and hospitalization (23 vs. 7, P<0.001). These observations, coupled with no evidence of physiological or clinical benefit for combination therapy, prompted the independent data and safety monitoring board to recommend termination of the combination-therapy group at a mean follow-up of 32 weeks. Data from the ongoing comparison of the NAC-only group and the placebo group are not reported here.

CONCLUSIONS

Increased risks of death and hospitalization were observed in patients with idiopathic pulmonary fibrosis who were treated with a combination of prednisone, azathioprine, and NAC, as compared with placebo. These findings provide evidence against the use of this combination in such patients. (Funded by the National Heart, Lung, and Blood Institute and the Cowlin Family Fund; ClinicalTrials.gov number, NCT00650091.)

Should IPF be treated with CS monotherapy?

- No RCT conducted,no survival benefit in retrospective studies.
- Recommendation(strong): CS monotherapy should not be used
- High value on treatment related morbidity

Combination CS & Immunomodulator? (azathioprine/cyclophosphamide)

- Recent studies show no survival benefit.
- Recommendation(strong): should not be treated with CS/Immunomodulator
- Preventing treatment related morbidity

Anticoagulants?

- JAPANESE trial: compared oral CS+WARFARIN to CS alone, survival benefit demonstrated
- But Low quality study
- Potential bleeding risk
- Hence Earlier Recommendation(weak):should not be used in majority, but reasonable in minority.

A Placebo-Controlled Randomized Trial of Warfarin in Idiopathic Pulmonary Fibrosis

Imre Noth[1], Kevin J. Anstrom[2], Sara Bristol Calvert[2], Joao de Andrade[3], Kevin R. Flaherty[4], Craig Glazer[5], Robert J. Kaner[6], and Mitchell A. Olman[7]; for the Idiopathic Pulmonary Fibrosis Clinical Research Network (IPFnet)*

[1]University of Chicago, Chicago, Illinois; [2]Duke Clinical Research Institute, Durham, North Carolina; [3]University of Alabama, Birmingham, Alabama; [4]National Jewish Medical Center, Denver, Colorado; [5]University of Texas Southwestern, Dallas, Texas; [6]Weill Cornell Medical College, New York, New York; and [7]Cleveland Clinic, Cleveland, Ohio

- RCT of Warfarin (INR 2-3) vs placebo
- No benefit
- Increased mortality
- Prematurely stopped
- Hence Recommendation now: Strong NO

Should COLCHICINE be used?

- Inhibit fibroblast proliferation,collagen synthesis
- Prospective clinical trials without any benefit
- Recommendation(strong): should not be used
- Low quality evidence

Should CYCLOSPORIN A be used?

- Recent studies shows no benefit
- Recommendation(strong): not to be used
- Prevention of side effects & cost

IFN-γ1b?

- Antifibrotic and immunomodulator
- Studies: no difference in mortality
- Recommendation(strong): should not be used

BOSENTAN?

- Dual endothelin receptor (A & B) antagonist
- Elevated endothelin in serum & BAL in IPF pts
- Studies : ongoing..
- Recommendation(strong):should not be used
- Potential risk,high cost

ETANERCEPT?

- Recombinant soluble human TNF,binds to TNF receptor & neutralises its activity.
- Studies:no significant trends
- Recommendation(strong): should not be used
- Potential risk,cost.

Therapies without recommendations

- SILDENAFIL:No significant difference in endpoint
- IMATINIB(tk inhibitor against PDGF):no meaningful difference in secondary endpoints

Non pharmacological therapies

LONG TERM OXYGEN THERAPY(LTOT)

Studies: clear survival benefit

Recommendation(STRONG): Pts with significant resting Hypoxemia should be treated with LTOT

LUNG TRANSPLANTATION

- 5 year survival benefit after lung transplantation **: 50-56%**
- No data to guide precise timing
- Recommendation(strong):appropriate Pts should undergo **LUNG TRANSPLANTATION**

Pulmonary rehabilitation?

- Aerobic conditioning,strength & flexibility training,nutritional interventions,psychosocial support
- Studies: improvement in walk distance and QOL
- Recommendation(weak):majority should be treated with Pulmonary rehabilitation

Treatment of selected complications & comorbid conditions

- Acute exacerbation
- Pulmonary hypertension
- Gastroesophageal reflux disease
- Obesity
- Emphysema
- Obstructive sleep apnea
- No data to make recommendations for obesity,emphysema,OSA treatment in IPF setting

PH & IPF

- Mean PAP >25 mmHg on right heart catheterisation
- Recommendation(weak): PH should not be treated in majority of Pts
- Cost & drug related morbidity
- Moderate to severe PH(>35 mmHg),trial of vasomodulatory therapy indicated.
- IV EPOPROSTENOL,ORAL BOSENTAN,SILDENAFIL improved pulmonary hemodynamics

Asymptomatic GERD treatment?

- Abnormal GER highly prevalent in IPF (87%)*
- 50% asymptomatic
- Risk of aspiration and pneumonitis present
- Recommendation(weak): should be medically treated in majority as there is no significant harm
- Recommendation does not extend to fundoplication.**

*High prevalence of abnormal acid gastro-oesophageal reflux in IPF
G. Raghu ERJ 2006
**Laparoscopic fundoplication in patients with end-stage lung disease awaiting transplantation Philip Lenden et al 2006

PALLIATIVE CARE

- Psychological & spiritual support
- COUGH- CS & Thalidomide
- Opioids – for severe dyspnea & cough

ACUTE EXACERBATION

- Acute respiratory worsening in **5-10%.**
- When cause cannot be identified.
- Data do not suggest infectious etiology.
- Unexplained worsening of **DYSPNEA** within 1 month,evidence of **HYPOXEMIA** or **impaired GAS EXCHANGE**,new radiographic **alveolar infiltrates** with Pneumonia,PNX,PE,HF ruled out.
- No known risk factors
- ↑ after BAL,thoarcic surgery
- Histology: acute/organising **DAD**

Acute exacerbation & CS?

- High dose CS commonly prescribed
- No controlled trials to judge efficacy
- Recommendation(weak):majority of Pts(Ex) should be treated with CS.
- Specific recommendations regarding DOSE,ROUTE,DURATION not made
- IV CS upto 1 gram/day reported beneficial

MV in IPF pts with respiratory failure

- Studies: high hospital mortality rate (96%)
- The only survivor in one study underwent lung transplantation 6 hours after intubation
- Recommendation(weak): should not receive MV,but reasonable choice in a minority of Pts
- High mortality rate to be explained to Pts,caregivers ahead of time
- NIPV appropriate in some Pts
- Can be used as a **BRIDGE to lung transplantation**

MONITORING CLINICAL COURSE

- Progressive disease
- Worsening symptoms
- Worsening oxygenation
- Complications & comorbidities

Monitoring for progressive disease

Any of the following changes consistent with progressive disease:

- Progressive dyspnea (objectively assessed)
- Progressive, sustained decrease from baseline in absolute FVC
- Progressive, sustained decrease from baseline in absolute DLCO (corrected for hemoglobin)
- Progression of fibrosis from baseline on HRCT
- Acute exacerbation
- Death from respiratory failure

Monitoring for worsening symptoms

- Eg: Dyspnea worsening has important management implications
- Dyspnea scoring (california university SOB questionaire)
- Assessment of oxygenation
- Detection of 2^{o} complications (DVT,PE)

Monitoring for worsening oxygenation

- Pulse oximetry @ rest & exertion
- Desaturation below 88% during 6MWT require supplemental oxygen
- Should be performed at baseline and 3-6 month intervals.
- Absolute **FVC change of 10%**
- Absolute **DL_{CO} change of 15%** surrogate marker of mortality & disease progression
- Others:TLC,P(A-a)0_2

Monitoring complications & comorbidities

- PH,PE,LUNG CA,CAD
- PH – consider lung transplantation
- Echocardiography inaccurate in estimating pulmonary hemodynamics in fibrotic lung disease
- Right heart catheterisation preferred
- BNP correlate with mod to severe PH

TREATMENT ASSESMENT PLAN

Patient status	6 months	12 months	More than 18 months
Worse	Treatment is stopped or changed	Consider an alternative therapy or lung transplantation	Consider an alternative therapy or lung transplantation
Improved or stable	Continue using the same doses of the medication(s)	Continue using the same doses of the medication(s)	Therapy be continued indefinitely and individualized on the basis of the clinical response and tolerance

CONCLUSION

- **A specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP.**

- The accuracy of the diagnosis of IPF increases with **multidisciplinary discussion** between pulmonologists, radiologists, and pathologists experienced in the diagnosis of ILD.
- IPF is a fatal lung disease; the natural history is variable and unpredictable:

a. Most patients with IPF demonstrate a **gradual worsening of lung function** over years; a minority of patients remains stable or declines rapidly.

b. Some patients may experience **episodes of acute respiratory worsening** despite previous stability.

- sub-clinical or overt comorbid conditions **pulmonary hypertension,gastroesophageal reflux, obstructive sleep apnea, obesity, and emphysema**.
- The impact of these conditions on the outcome of patients with IPF is unclear

- The recommendation against the use of the following agents for the treatment of IPF is strong:
- CS MONOTHERAPY
- COLCHICINE
- CYCLOSPORIN A
- Combined ACETYL CYSTEINE,AZATHIOPRINE,PREDNISONE
- COMBINED CS & IMMUNOMODULATOR
- IFN γ 1b
- BOSENTAN
- ETANERCEPT
- WARFARIN

- Following therapies may be a reasonable choice in a minority:
- PIRFENIDONE
- ACETYLCYSTEINE MONOTHERAPY
- ANTICOAGULANTS

- **Long-term oxygen therapy** recommended in patients with IPF
- The recommendation for **lung transplantation** in appropriate patients with IPF is strong.
- **Mechanical ventilation** should not be used in the majority of patients with IPF.
- **Pulmonary rehabilitation** should be used in the majority of patients with IPF.

- **Corticosteroids** should be used in the majority of patients with acute exacerbation of IPF.
- **Pulmonary hypertension** should not be treated in the majority of patients with IPF.
- Asymptomatic **gastroesophageal reflux** should be treated in the majority of patients with IPF.